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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,211	FORD ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/06 10/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. The election **without traverse** filed March 27, 2009, is acknowledged and has been entered.

Applicant has elected the invention of Group I, drawn to a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1; (b) exposing a biological sample from said mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in said biological sample the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer. Furthermore, Applicant has elected the species of S100A9 as the species of biomarker from Table 1. Because applicant did not distinctly and specifically point out the supposed errors in the species requirement, the species election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-2 are pending in the application. Claim 2 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claim 1 is under examination.

Information Disclosure Statement

4. The references cited in the information disclosure statements filed on December 6, 2006, and October 14, 2008, have been considered.

Priority

5. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of US provisional application 60/556,903 filed March 26, 2004, is acknowledged.

However, claim 1 does not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since that claim is rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claim is deemed the filing date of PCT/US05/10454, namely March 28, 2005.

Specification

6. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is RNA*later*® (see, e.g., paragraph 100).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic

terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

7. Claim 1 is objected to for reciting Table 1. MPEP 2173.05(s) states:

> "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

In this case, the biomarkers set forth in Table 1 could easily be incorporated in to the claim to define the invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 1 is vague and indefinite in the recitation "measuring *in the mammal* the level of at least one biomarker" because it is unclear whether the measurement step occurs *inside the mammal,* or if measuring *in the mammal* includes measurements of biomarkers that occur outside the mammal in a biological sample. Accordingly,

because it is unclear or cannot be ascertained where the measuring step occurs, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

(b) Claim 1 is also indefinite because of the use of the terminology "EGFR", as the sole means to identify the "EGFR modulator" in the claimed methods. The use of such laboratory designations to identify a gene/protein renders the claim indefinite because different laboratories may use the same nomenclature to identify structurally and/or functionally distinct gene products, such as, e.g., orthologs, paralogs, and homologs that are perhaps produced by different types of cells, tissues, or animals (including, e.g., human, horse, cow, pig, mouse, rat, frog, etc.), or perhaps genes/proteins that are all together different and lack any apparent structural or functional relationship. Furthermore, the recitation of the term "modulator" is unclear because different EGFR genes/proteins have many different functions, and it cannot be determined which functions of EGFR genes/proteins must be modulated. Must expression, activity, location of "EGFR" be modulated or must "EGFR" be modulated in some other way? Accordingly, because it is unclear or cannot be ascertained to which of the different genes/proteins termed "EGFR" the claims are directed or which activity is "modulated", it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

(c) As drawn to the elected species, Claim 1 is also indefinite because of the use of the terminology "S100A9", as the sole means to identify the biomarker in the claimed methods. The use of such laboratory designations to identify a gene/protein renders the claim indefinite because different laboratories may use the same nomenclature to identify structurally and/or functionally distinct gene products, such as, e.g., orthologs, paralogs, and homologs that are perhaps produced by different types of cells, tissues, or animals (including, e.g., human, horse, cow, pig, mouse, rat, frog, etc.),

or perhaps genes/proteins that are all together different and lack any apparent structural or functional relationship. Notably, while Table 1 identifies a nucleotide sequence and an amino acid sequence for a "S100A9" nucleotide and protein it is unclear if these sequences are to be the sequences of the "S100A9" nucleotide and protein being measured or if they are just exemplary of an "S100A9" biomarker.

It is suggested that this issue be remedied by amending claim1 to recite a limitation identifying the nucleotide and/or amino acid sequence of the "S100A9" biomarker being referred to by SEQ ID NO, which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the biomarker to which the claim is directed.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this case, the claim is broadly drawn to diverse methods for identifying a diverse genus of "mammals" that will respond therapeutically to a method of treating a diverse genus of "cancers" comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in *the mammal* the level of at least one biomarker selected from the biomarkers of Table 1; (b) exposing a diverse genus of "biological samples" from said mammal to a structurally and functionally diverse genus of "EGFR modulators"; (c) following the exposing of step (b), measuring in said "biological sample" the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer. Furthermore, as drawn to the elected species of invention, the species of biomarker from Table 1 is a structurally and functionally diverse genus of molecules designated "S100A9".

Notably, as a first point the claim is broadly drawn to methods comprising exposing a biological samples from a mammal to a structurally and functionally diverse genus of "EGFR modulators". In this case, the claims do not require that the "EGFR modulators" possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature except for some ability to "modulate" an "EGFR" gene/protein.

The specification teaches in page 37 the following about "EGFR modulators":

> As used herein, the term "EGFR modulator" is intended to mean a compound or drug that is a biological molecule or a small molecule that directly or indirectly modulates EGFR activity or the EGFR signal transduction pathway. Thus, compounds or drugs as used herein is intended to include both small molecules and biological molecules. Direct or indirect modulation includes activation or inhibition of EGFR activity or the EGFR signal transduction pathway. In one aspect, inhibition refers to inhibition of the binding of EGFR to an EGFR ligand such as, for example, EGF. In another aspect, inhibition refers to inhibition of the kinase activity of EGFR.
>
> EGFR modulators include, for example, EGFR-specific ligands, small molecule EGFR inhibitors, and EGFR monoclonal antibodies. In one aspect, the EGFR modulator inhibits EGFR activity and/or inhibits the EGFR signal transduction pathway. In another aspect, the EGFR modulator is an EGFR monoclonal antibody that inhibits EGFR activity and/or inhibits the EGFR signal transduction pathway.
>
> EGFR modulators include biological molecules or small molecules. Biological molecules include all lipids and polymers of monosaccharides, amino acids, and nucleotides having

> a molecular weight greater than 450. Thus, biological molecules include, for example, oligosaccharides and polysaccharides; oligopeptides, polypeptides, peptides, and proteins; mad oligonucleotides and polynucleotides. Oligonucleotides and polynucleotides include, for example, DNA and RNA.
>
> Biological molecules further include derivatives of any of the molecules described above. For example, derivatives of biological molecules include lipid and glycosylation derivatives of oligopeptides, polypeptides, peptides, and proteins.
>
> Derivatives of biological molecules further include lipid derivatives of oligosaccharides and polysaccharides, e.g., lipopolysaccharides.

Accordingly, while the “EGFR modulator” must be capable of "modulating" EGFR in some manner, the specification does not describe with any particularity the identifying structural and/or functional features of the genus of “EGFR modulators”, which include derivatives of any of the molecules described and may otherwise have any structure so long as they somehow “modulate" EGFR. In this case, the specification, does not describe the structure of a sufficient number of species of the genus of “EGFR modulators”, to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Notably, while the exposing step is broadly drawn to any “EGFR modulator” that can "modulate" EGFR, i.e., increase or decrease EGFR in some way, the art has only identified a relatively few epidermal growth factor receptor *inhibitors* which can treat only certain types of epithelial cancers. For example, Harari et al (JCO, 26(26)4057-4065, 2007) only teach 2 species of antibodies and 3 species of tyrosine kinase inhibitors that are epidermal growth factor receptor inhibitors which can be used to treat certain cancers in some mammals, but not all cancers in every mammal (see entire document, e.g., abstract and pages 4061 and 4062). Furthermore, Harari et al teach that while these antibody inhibitors and tyrosine kinase inhibitors both can be effective in treating certain cancers that “specific mechanisms of action for each anti-EGFR class also vary in several subtle but important ways” (see page 4061, right column). Accordingly, because each different modulator would have different mechanisms of action they would also differently affect expression of biomarkers so that one of skill in the art could not immediately envision, recognize or predict if a “biomarker” identified using one modulator would also have the same change in expression using a different modulator with a different mechanism of

action. Accordingly, it is apparent that one of skill in the art could not immediately envision, recognize or predict which of the diverse genus of "EGFR modulators" encompassed by the claims could be exposed to a biological sample to identify a mammal that will respond therapeutically to a method of treating cancer comprising administering the "EGFR modulator" by measuring and comparing expression of biomarkers from Table 1 or a "S100A9" biomarker from a mammal and a biological sample exposed to the "modulator". In this case, it is apparent that it is highly unpredictable whether any method with any "EGFR modulator" encompassed by the claims would be able to identify a mammal that will respond therapeutically to a method of treating cancer comprising administering the "EGFR modulator". Thus, one of skill in the art would not immediately envision which members of the "EGFR modulator" genus would be suitable for the claimed method given the written description provided by the specification and one of skill in the art would not recognize that applicant was in possession of the claimed methods.

The Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to

distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004).

For these reasons, as a whole, it is submitted that the specification would amount to no more than a mere invitation to the skilled artisan to *discover* the identity of other "EGFR modulators" which are effective in the recited method by screening for other compounds that modulate EGFR and are also shown to be effective in treating cancer to see if such other "EGFR modulators" encompassed by the claims *exist*, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for identifying it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of "EGFR modulators", which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual

reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

For these reasons because the skilled artisan could not immediately envision, recognize or distinguish which, if any, "EGFR modulators" would be effective to achieve the claimed intended results, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed methods at the time the application was filed.

Secondly, it is also noted that the claims are drawn to measuring biomarkers in a diverse genus of "biological samples" which are not explicitly defined in the specification but can include, for example, serum, whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, skin, hair follicle, bone marrow, or tumor tissue (see page 4).

In this case, while the specification characterizes that mRNAs of a gene designated "S100A9" comprising the nucleic acid sequence of SEQ ID NO:10 are present in lung cancer cells lines (see page 48), it is established in the art that there is a high degree of unpredictability in extrapolating the presence of an mRNA and/or protein in one "biological sample" with the presence of that mRNA and/or protein in another sample and cannot be predicted *a priori.* For example, Roessler et al (a) (Mol. Cell. Prot., 5(11):2092-2101, 2006) teach that of five proteins identified as elevated in colorectal cancer tissue samples as compared to normal colorectal samples only one of these proteins could be shown to be elevated in serum samples obtained from individuals with colorectal cancer (see entire document, e.g., page 2099, right column). Additionally, Roessler et al (b) (Clin. Can. Res., 11(18):6550-6557, 2005) teach that while proteins may be elevated in tissue samples obtained from individuals with colorectal cancer, "which of the cancer-associated proteins found in tumor tissue that eventually will be present in serum or plasma cannot be predicted *a priori".* Finally, Zolg

et al (Mol. Cell. Prot., 3(4):345-354, 2004) teach when commenting on whether proteins identified as elevated in cancer tissue screens will also be elevated in liquid samples obtained from individuals that "[an] inherent risk in the tissue approach is the fact that the candidate marker identified in e.g., tissue cannot later be detected in peripheral fluid such [as] serum" (see entire document, e.g. page 347, right column , 1st paragraph). While Roessler et al (a) and (b) pertain to biomarkers for colorectal cancer, it is apparent that these teachings are relevant to the instant case because one of skill in the art could not immediately envision whether the expression of mRNAs of a gene designated "S100A9" comprising the nucleic acid sequence of SEQ ID NO:10 in cell lines would extrapolate to the S100A9 protein encoded by that mRNA being present in e.g., urine or plasma samples. Additionally, as drawn to the elected species of a molecule designated "S100A9", which as set forth in the above rejection of the claims under 35 USC 112, second paragraph might refer to multiple structurally and functionally distinct nucleic acids and/or proteinsm, one of skill in the art also would not be able to immediately envision, recognize or predict which other biomarkers encompassed by the "S100A9" genus might be detected in such diverse sample.

Furthermore, it should also be noted that the claims are drawn to measuring the level of the biomarker after exposing the sample to the EGFR modulator, and the specification does not establish that exposing e.g., a urine sample to a EGFR modulator would have any effect on the "level" of the biomarker in the urine sample. Notably, *arguendo,* if a "biomarker" were present in a "biological sample" such as a urine sample, exposing that sample to some other agent would not be expected to alter the level of the "biomarker" in that sample because the level of the "biomarker" in the sample was set before the sample was exposed to the modulator. Notably, this is different from a cell line sample which can upregulate or downregulate expression of genes in response to being exposed. Accordingly, for these reasons as well it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed methods at the time the application was filed.

Finally, it is noted the claim recites that "a *difference* in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker

measured in step (a) *indicates that the mammal will respond therapeutically* to said method of treating cancer". Notably, while the claims do not even require the levels from step (a) and (c) to be compared between two corresponding samples from the mammal, one of skill in the art would also not recognize that Applicant was in possession of the claimed methods because the specification has not established that measuring and comparing the levels of any molecule designated "S100A9" in methods as set forth in the claimed method results in "a difference that *indicates that the mammal will respond therapeutically* to said method of treating cancer". In this case, over pages 46 through 48 the specification indicates that the levels of mRNAs of the molecules in Table 1, which includes a gene designated "S100A9" comprising the nucleic acid sequence of SEQ ID NO:10 are gene sequences that "showed a significantly different expression profile between the sensitive and resistant cell lines with a p-value of 0.05" (see page 48). It appears that the recited cell lines were established from *different* lung cancers that are either resistant or sensitive to the epidermal growth factor receptor inhibitor, cetuximab (see page 47, line 2). Nowhere does the specification determine whether the claimed method indicates that the mammal will respond therapeutically to said method of treating cancer by a mere difference in the level of any biomarker. Notably, one of skill in the art would not consider a mere difference in the level of a biomarker in two samples to be predictive of anything because assays that determine levels of biomarkers are highly variable. Accordingly, even if one sample is split into two and assayed separately there would be some variance, i.e., difference in the two levels due to the inherent variability of the assays. While the two levels might be very close and not statistically significant, there would still be "a difference" in the levels. Secondly, it is established in the art that there is a high degree of unpredictability in identifying biomarkers that predict sensitivity of cancer to a treatment "drug" by determining a "difference" in levels of the biomarker in two samples one of which has been exposed to "drug" and one that has not. For example, of particular importance in this case, Zembutsu et al (Int, J. Can. 23:29-39, 2003, IDS filed 10/14/2008) monitored expression changes of genes up and down regulated by the epidermal growth factor receptor inhibitor, ZD1839 using a genome-

wide cDNA microarray consisting of 23,040 genes and compared sensitive lung cancer cell line samples, one before treatment and one after treatment to identify genes up or down regulated by the treatment in the sensitive cell lines and also compared resistant lung cancer cell line samples, one before treatment and one after treatment to identify genes up or down regulated by the treatment in the resistant cell lines and found that the same genes which were up or down regulated by the treatment in the sensitive cell lines also “tended to be induced or suppressed in the resistant samples" (see entire document, e.g., page 35, right column). Accordingly, it is apparent that one of skill in the art could not immediately envision, recognize or predict if the genes identified in the instant application by comparing expression profiles between the sensitive and resistant cell lines would also be biomarkers that predict the sensitivity of a cancer to any “EGFR modulator” since their expression may also be similarly altered in resistant cancers.

In summary, it is submitted that the specification would amount to no more than an invitation to the skilled artisan to discover the identity of processes encompassed by the claims. In this case, because of the lack of particularly with which the claimed methods are described, one of skill in the art would not consider that the disclosure is representative of the claimed methods and it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed methods at the time the application was filed.

12. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** methods comprising steps as encompassed by the claims that have been disclosed in the prior art, **does not reasonably provide enablement for using** the claimed methods to achieve the recited objective of identifying a mammal that will respond therapeutically to a method of treating cancers comprising administering an EGFR modulator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In this case, the claim is broadly drawn to diverse methods for identifying a diverse genus of "mammals" that will respond therapeutically to a method of treating a diverse genus of "cancers" comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in *the mammal* the level of at least one biomarker selected from the biomarkers of Table 1; (b) exposing a diverse genus of "biological samples" from said mammal to a structurally and functionally diverse genus of "EGFR modulators"; (c) following the exposing of step (b), measuring in said "biological sample" the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker

measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer. Furthermore, as drawn to the elected species of invention, the species of biomarker from Table 1 is a structurally and functionally diverse genus of molecules designated "S100A9".

For the reasons set forth in the above rejection of the claims, as failing to satisfy the written description requirement, it has been submitted that the specification would amount to no more than an invitation to the skilled artisan to discover the identity of other processes encompassed by the claims.

Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

As explained in the above rejection of the claims, as failing to satisfy the written description requirement, because the claims are directed to processes reciting a genus of "EGFR modulators" that have not been described so as to permit the skilled artisan to immediately envision, recognize or distinguish the "structure" of the members of this genus which would be effective to modulate "EGFR", the skilled artisan also could not make these "agents" or "antibodies" without undue and/or unreasonable experimentation; and if these "agents" or "antibodies" cannot be made without undue and/or unreasonable experimentation, the specification would not reasonably enable the skilled artisan to use the claimed processes without undue experimentation.

Secondly, as set forth in the above written description rejection, Zembutsu et al (supra) evidence that there is a high degree of unpredictability in identifying a mammal that will respond therapeutically to a method of treating cancers comprising

administering an EGFR modulator because Zembutsu et al teach that the same genes which were up or down regulated by treatment in ZD1839 sensitive cell lines also "tended to be induced or suppressed in the [ZD1839] resistant samples" (see entire document, e.g., page 35, right column). Notably, in this case, the specification does not present any specific non-general guidance that methods encompassed by the claims would be able to identify a mammal that will respond therapeutically to a method of treating cancers comprising administering an EGFR modulator because the specification only establishes the molecules in Table 1, which includes a gene designated "S100A9" comprising the nucleic acid sequence of SEQ ID NO:10 are gene sequences that "showed a significantly different expression profile between the sensitive and resistant cell lines with a p-value of 0.05" (see page 48). Accordingly, while one of skill in the art would be able to measure and compare the levels of the molecules having the sequences set forth in any number of samples, they would be subject to undue and unreasonable experimentation to use the claimed methods to achieve the clamed objective of identifying a mammal that will respond therapeutically to a method of treating cancers comprising administering an EGFR modulator because every comparison would result in some difference in biomarker level and it is apparent from Zembutsu et al that differences in levels are not predictive of the mammals which will respond to treatment. For this reason, if it were one's objective to identify mammals that will respond to a method of treating cancers comprising administering an EGFR modulator, it is submitted that it would not suffice to practice the claimed process steps as one would not achieve the claimed objective by simply doing so.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Zembutsu et al (Int. J. Onc., 23:29-39, 2003, IDS filed 10/14/2008) as evidenced by Exhibit A.

As drawn to the elected invention the claim is herein drawn to methods comprising (a) measuring in a mammal the level of a biomarker designated "S100A9"; (b) exposing a biological samples from said mammal to a EGFR modulators; (c) following the exposing of step (b), measuring in said biological sample the level of the biomarker designated "S100A9", wherein a difference in the level of the biomarker designated "S100A9" measured in step (c) compared to the level of the biomarker designated "S100A9" measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer. Notably, as explained in the above rejection of the claim under 35 USC 112, second paragraph, the phrase "measuring in the mammal" is indefinite, accordingly, the phrase is being broadly but reasonably interpreted to include measuring levels of a biomarker designated "S100A9" in a sample from a mammal.

Zembutsu et al teach methods of measuring in lung cancer cell line samples from a mammal the levels of 23,040 genes and exposing a lung cancer cell line sample to the epidermal growth factor receptor inhibitor, ZD1839, i.e., a "EGFR modulator" and measuring the levels of 23,040 genes in this sample and then comparing the levels to identify genes up or down regulated by the treatment to one before treatment and one after treatment to identify genes up or down regulated by the treatment with ZD1839. Zembutsu et al also teach that these 23,040 genes are a 'genome-wide' cDNA microarray system available from the NCBI database. Notably, as evidenced by Exhibit A, a gene designated "S100A9" was placed in the NCBI database in 1999 so the

methods of Zembutsu et al which look at 23,040 genes from a 'genome-wide' cDNA microarray from this database would inherently monitor levels of a biomarker structurally and materially indistinguishable from the elected "S100A9" species. Furthermore, while the methods of Zembutsu et al do not expressly set forth "a difference" in the levels of this gene in the two samples, the method of Zembutsu et al would have inherently identified a difference because the method is manipulatively and materially indistinguishable from the claimed method. Finally, while Zembutsu et al is silent as to whether identifying a difference in a gene designated "S100A9" indicates that the mammal will respond therapeutically to said method of treating cancer, it is noted that this is an inherent feature of the instant claim because it recites that it is the *difference* that indicates that the mammal will respond therapeutically to said method of treating cancer.

Therefore, the processes of Zembutsu et al are manipulatively and materially indistinguishable from the instantly claimed methods. Accordingly, because the methods disclosed in the prior art are manipulatively and materially indistinguishable from the instantly claimed methods, absent a showing of any difference, the claimed methods and the methods disclosed by the prior art are deemed the same and Zembutsu et al anticipate the claimed method.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571)272-9935. The examiner can normally be reached on 7-4:30 M-F with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
June 19, 2009